NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Brill:

Please refer to your new drug application (NDA) dated December 15, 1998, received December 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (aspirin/extended-release dipyridamole) Capsules.

We acknowledge receipt of your submissions dated June 18, 21, and 30, July 12, August 2, 6, 11, 13, and 20, September 8, October 6 and 20, November 3, 4, 11, 12, and 16, 1999. In addition, we acknowledge receipt of your facsimiles dated November 17, 18, and 19, 1999. Your submission of August 20, 1999, constituted a complete response to our June 15, 1999, action letter.

This new drug application provides for the use of Aggrenox™ (aspirin/extended-release dipyridamole) Capsules to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted
December 15, 1998, and October 20, 1999, respectively). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-884." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 20, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. Conduct a food effect study to evaluate the effect of food/meals on the absorption of dipyridamole and aspirin, and to assess the potential for "dose-dumping" of the extended release dipyridamole pellets of the to-be-marketed Aggrenox™ Capsules. You agreed to submit study results and appropriate labeling revisions by February 20, 2000.

2. Conduct a study to provide information/data comparing the dipyridamole pharmacokinetics obtained in subjects receiving (a) the to-be-marketed Aggrenox™ Capsule, and (b) the FDA approved immediate release dipyridamole formulation given concurrently with the aspirin tablet that is included in the Aggrenox™ Capsule to substantiate the extended release claim for the dipyridamole pellet component. You agreed to submit study results and appropriate labeling revisions within 12 months of initiation of the study.

Please submit protocols, data and final reports to this NDA as correspondence. In addition, under
21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Sufficient stability data has been submitted to support an 18-month expiry date for the 60-count polypropylene bottles.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research